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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	11

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/776,938	HUMAN
	Examiner	Art Unit
	GAMBEL	1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/6/03

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) ____ is/are pending in the application. 1, 5-13, 16-17, 19-27

4a) Of the above claim(s) ____ is/are withdrawn from consideratio

5)☐ Claim(s) ____ is/are allowed.

6)☑ Claim(s) ____ is/are rejected. 1, 5-13, 16-17, 19-27

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requireme

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 1/6/03 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on ____ is: a)☐ approved b)☐ disappr d by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

PAPER NO. 11

DETAILED ACTION

1. Applicant's amendment, filed 1/2/03 (Paper No. 9), has been entered.
Claims 2-4, 14-15 and 18 have been canceled. Claims 42-56 have been canceled previously.
Claims 1, 5-13 and 16 have been amended.
Claims 19-27 have been added.

Claims 1, 5-13, 16-17 and 19-27 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 1/2/03 (Paper No. 9).
The rejections of record can be found in the previous Office Action (Paper No. 8).

3. Formal drawings submitted 1/2/03 comply with 37 CFR 1.84.

4. Claims 1, 5-13, 16-17 and 19-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kaminski et al. (U.S. Patent No. 6,287,537) AND/OR Anderson et al. (U.S. Patent No. 5,843,439) in view of Gruss et al. (Leukemia and Lymphoma 24: 393-422, 1997), Carbone et al. (Am. J. Pathol. 147: 912- 922, 1995), Black et al. (U.S. Patent No. 6,001,358), in view of standard chemotherapeutic treatments, including combination therapy of malignancies, including lymphomas known and practiced by the ordinary artisan at the time the invention was made, as acknowledged on pages 41-45 of the instant specification essentially for the reasons of record set forth in the previous Office Action (Paper No. 8)..

Applicant's arguments, filed 1/2/03 (Paper No. 9), have been fully considered but are not found convincing essentially for the reasons of record and addressed herein.

Applicant asserts that the claimed invention relies upon the unexpected discovery that administration of an antibody that antagonizes the interaction of CD40 and CD40L unexpectedly and synergisticaly enhances the anti-lymphoma activity of an anti-CD20 antibody. Applicant further asserts that at the time the invention was filed that it was not known that the combination of these two antibodies would interact synergistically to kill lymphoma cells. Applicant relies upon the results set forth in the instant Figure 2b, Table I of Example 3 for the increased cytotoxicity and apoptosis of B lymphoma cells with the combination of anti-CD20 antibodies and blocking interaction between CD40 and CD40L.

Applicant further asserts that the combination therapies with two different antibodies were not described by the prior art and cites that Rituxan was the first antibody to be approved for treatment of B cell malignancy to support the uncertainties and unpredictability was associated with the use of antibodies for therapy.

As pointed out previously, Kaminski et al. teach the use of anti-CD20 antibodies, including radiolabeled anti-CD20 antibodies (e.g. B1) in combination with other treatments to treat B cell malignancies, including non-Hodgkin's lymphoma (e.g. column 8, paragraph 1) (see entire document, Summary of the Invention and Detailed Description of the Invention). Kaminski et al. teach various modes of dosages and administration that were well known to those of skill in the art in the treatment of B cell malignancy (e.g. see columns 9-12 and Examples), encompassed by the claimed invention.

Also, Anderson et al. teach the use of anti-CD20, including radiolabeled anti-CD20 antibodies (e.g. 2B8 in cooperative strategies to treat B cell malignancies, including non-Hodgkin's lymphoma (e.g. column 3, paragraph 2) (See entire document, including Background of the Invention, Summary of the Invention, Detailed Description of the Invention, Claims).

Therefore in contrast to applicant's assertions, the prior art taught combination therapy to various B cell malignancies, including B cell non-Hodgkin's lymphoma with CD20-specific antibodies at the time the invention was made. Providing radiotherapy and chemotherapy was known and routinely practiced at the time the invention was made in the treatment of non-Hodgkin's lymphomas at the time the invention was made.

In contrast to applicant's assertions of unexpected synergistic results, the following is noted. The role of the anti-CD20 antibody and the blocking the interaction between CD40 and CD40L in treating B cell malignancy differ. Here, the prior art of Carbone et al. and Gruss et al. taught the importance of CD40L-mediated interactions in B cell non-Hodgkin's lymphoma and clinical manifestations of lymphoma growth and therapeutic intervention. Also as pointed out above, Gruss et al. does teach that CD40:CD40L interactions are part of cellular activation and neoplastic tumor cell growth which would be useful for the therapeutic management of $CD40^+$ tumors (see page 404, column 1). Further, applicant appears to rely upon certain experimental conditions with certain cell lines to support their assertions of unexpected results. However, these results do not appear to be inconsistent with the expected roles of blocking CD40 interaction with CD40L and targeting CD20 in the treatment of B cell malignancy, including B cell non-Hodgkin's lymphoma, taught by the combination of references in the prior art.

As pointed out previously, Carbone et al. teach the expression of CD40 on B cell non-Hodgkin's lymphoma and CD40 ligand expressing cells T cells were detected within neoplastic follicles and surrounding areas via immunohistochemistry analysis (see entire document, particularly page 917; B-Cell NHL). Carbone et al. also discuss the role such CD40 ligand expressing T cells on CD40 expressing B cell lymphoma proliferation (See Discussion, particularly page 920, column 1, paragraph 1).

Also, Gruss et al. teach that CD40 is expressed on B cell lymphomas and that the CD40:CD40L pathway, including CD40L-expressing T cells, which are readily detectable around neoplastic B cells, enhance B cell activation and growth (see pages 404-405, B cell Lymphomas and Lymphoproliferative Disorders and Discussion). Gruss et al. teach that the anti-proliferative and pro-apoptotic effects of recombinant CD40L on high grade B-NHLs offer an appealing biologic approach for treatment of these neoplasms (page 405, column 1). While Gruss et al. disclose the art known formation of neutralizing anti-mouse antibodies as a limitation of antibody therapy (page 405, column 1, lines 24-27), such limitations have been long addressed by the use of recombinant antibodies such as humanized antibodies, known and practiced in the art for a decade (also, see Black et al. herein).

Therefore, the role of anti-proliferative and pro-apoptotic effects of targeting CD40L on high grade B-NHLs offered an approach for treatment of these neoplasms was taught and known by the prior art teachings. It would have been expected that targeting CD40L on high grade B-NHLs would have left such cells more sensitive to treatment with anti-CD20 antibodies. Again, given the expression of CD20 and CD40 and the ability of activation via CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell non-Hodgkin's lymphoma directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation by CD40 ligand expressing T cells with CD40L-specific antibodies.

Given the teachings of Kaminksi et al. to employ radiolabeled antibodies in combination with other treatments to treat leukemia as well as the acknowledgment by applicant that combination therapy was known and practiced in the art at the time the invention was made, one of ordinary skill in the art would have been motivated to treat B cell leukemia with a combination of therapies.

Given the expression of CD20 and CD40 and the ability of activation via CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell non-Hodgkin's lymphoma directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation by CD40 ligand expressing T cells with CD40L-specific antibodies.

One of ordinary skill in the art would have employed non-radiolabeled CD40L-specific antibodies, given the expression of CD40L on normal activated T cells and the role of such CD40L on such T cells to stimulate CD40-expressing B cell lymphoma cells, as taught above.

Given the standard regimen of chemotherapy in leukemic patients and the teachings of Kaminski et al. to combine standard therapy with radiolabeled antibodies, one of ordinary skill in the art at the time the invention was made to employ multiple modalities to treat B cell lymphomas. Given the addition of non-radiolabeled CD40L-specific antibodies, the ordinary artisan would have been administering a less toxic therapeutic regimen, when compared to radiolabeled antibodies and chemotherapeutic agents.

One of ordinary skill in the art at the time the invention was made would have been motivated to select radiolabeled CD20-specific antibodies, non-radiolabeled CD40L-specific antibodies and standard chemotherapeutic to treat B cell lymphomas at the time the invention was made, given the teachings above. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

For the record, it is apparent that IDEC-C2B8 and Mab 24-31 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

Given the disclosure and the claims encompassing the instant IDEC-C2B8 and Mab 24-31 antibodies set forth in the claims of U.S. Patent Nos. 5,843,439 and 6,001,358.; the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to IDEC-C2B8 and Mab 24-31 appear to have been satisfied.

If applicant intends that IDEC-C2B8 and Mab 24-31 antibodies refer to antibodies other than that encompassed by the exact limitations of these patented claims, then the instant claims would be subject to a rejection under 35 USC 112, first paragraph, for the deposit of biological materials.

5. Claims 1, 5-13, 16-17 and 19-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims of copending application USSN 09/435,992 . Given the election in the instant case, the conflicting claims may or may not be identical, depending upon the invention(s) elected in these copending applications. The claims are not patentably distinct from each other because they appear to read on the same or nearly the same reagents to treat the same or nearly the same leukemias and lymphomas.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment, filed 1/2/03 (Paper No. 9), indicates that the rejection should be removed because the instant claims are drawn to lymphoma while the copending claims are drawn to leukemia.

Applicant is invited to clarify whether treating lymphoma and leukemia are patentably distinct. For example, applicant's election in Paper No. 6 indicated that the examiner would broaden the search and examination to all B cell lymphomas and leukemias.

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 7, 2003